REMARKS

Entry of the above amendments and reconsideration of the above-referenced application are respectfully requested. Of claims 11-93 originally pending, claims 11-69 and 79-93 are currently under consideration due to a restriction requirement wherein the Examiner has withdrawn claims 70-78. Various claims stand rejected under 35 U.S.C. § 112, first and/or second paragraph and under 35 U.S.C. § 102(b), 102(e) and 103(a) over various cited art. Applicant will discuss the rejections in the order provided in the Action. In view of the discussion below, it is believed that all rejections have been overcome. Applicant notes that the cross-reference to related applications has been updated in the first paragraph of the specification as requested by the Examiner. Entry of this paragraph in the application is respectfully requested.

Rejection of claims 32, 33, 36-47, 51-55, 57-66, 68, 69, 82, 85, 89 and 92 under 35 U.S.C. § 112, first paragraph

The above claims that include recitation of a genus of amino acid sequences sufficiently similar to SEQ ID NO:1 or SEQ ID NO:2, and of amino acid sequences that must exhibit a binding activity as claimed, are rejected as it is asserted that applicant's disclosure of one species of functionally active fibronectin does not provide sufficient description of the specific structures of a representative number of unspecified protein sequences other than functionally active fibronectin peptides that would support applicant's possession of the genus of amino acid sequences which must possess the claimed biological activities. It is further mentioned in the Action that an adequate written description of the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays identifying the agents. The claims are further rejected under this section wherein it is asserted in the Action that the specification is only enabling for claims limited to fibronectin or fibronectin fragments.

Applicant asserts that the specification is sufficiently detailed and allows one skilled in the art to practice the invention to the full breadth of the recited

claims without undue experimentation. For example, guidance as to amino acid sequences that exhibit the recited binding capacities may be found by identifying similar sequences, and routine procedures may be utilized, to determine whether the invention may be practiced with proteins having these sequences. Such routine procedures to determine whether the polypeptide has the desired binding activities are discussed, for example, on page 15, 17, and in Examples 8 and 9. Additionally, the biotechnological arts have advanced to the state where deletion, substitution, addition or other modification of amino acids in the subject functional domains can be routinely performed, as mentioned on page 17 of the application.

For example, it is known in the art that a given amino acid of one group (such as a non-polar amino acid, an uncharged polar amino acid, a charged polar acidic amino acid or a charged polar basic amino acid) may be substituted with another amino acid from the same amino acid group. Whether a given substitution will affect the functionality of the enzyme may be determined without undue experimentation using techniques and assays known in the art and described in the specification. As the application provides a sufficient written description and enables one skilled in the art to practice the invention to the full breadth as claimed, withdrawal of the rejection of the above-referenced claims under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Rejection of claims 24, 25, 32-37, 42, 44-51, 52-56, 61-66, and 84-86 under 35 U.S.C. § 112, first paragraph

In reference to the method of cellular grafting claims, it is asserted in the Action that the specification is enabling only for such claims relating to use of viable hematopoietic cells from a murine donor and fibronectin and/or a fragment thereof. It is further asserted that the specification does not teach the metes and bounds of a stated positive effect from the grafting methods. It is also mentioned in the Action that no details are provided for administration of the cells, such as numbers of cells needed for a particular disease or the route of administration for each application The Action further asserts that, in reference to the claims relating to methods of increasing the frequency of transduction of hematopoietic

cells, the specification is enabling only for methods that are practiced *in vitro* and with fibronectin and/or a fragment thereof.

As mentioned above, the specification provides sufficient guidance to one skilled in the art to practice the full scope of the pending claims. In reference to the cellular grafting claims, it is noted that applicant has amended claims 24, 44, and 62 to indicate that the donor and recipient are mammals, and claim 84 to indicate that the recipient is a mammal. Support for these amendments may be found, for example, on pages 19 and 20 of the specification.

Additionally, it is taught in the specification on page 20 that a route of administration of the cells may be, for example, intravenous. Other known routes of administration may be utilized by medical or other personnel depending on the situation. It is further taught on, for example, pages 20 and 21 of the specification that the methods may be used to treat a wide variety of disorders, including cancers, leukemias, and to improve resistance to other therapeutic protocols such as chemotherapy. Representative disorders that may be treated are taught on page 21 of the specification and include ADA deficiency, pediatric acute myelogenous leukemia (AML), neuroblastoma, adult AML and acute lymphocytic leukemia (ALL). Other disorders that may benefit from the methods recited in the pending claims are known to the skilled artisan. The specific dosage of cells, routes of administration, level of expression required and endpoints for determining the effectiveness of the protocol are known to the art using routine procedures that may be adjusted for a particular case without undue experimentation.

Furthermore, it is noted in the Action that Moritz et al. teach that gene transfer experiments "have met with limited success, largely because of the low efficiency of infection of primitive hematopoietic cells." As an initial point, "limited" success is more than enough for patenting purposes. Clinical utility is not the test. Additionally, one aspect of the present invention is the provision of improved transduction efficiencies. Greater success in grafting may be achieved when high transduction frequencies are obtained, and thus the invention squarely address the "limitedness" of the success achieved to date in the field.

In reference to the assertion that the specification only enables practice of claims relating to methods for increasing the frequency of transduction of viable hematopoietic cells with fibronectin and/or fragments thereof, the comments in support of the patentability of claims 32, 33, 36-47, 51-55, 57-66, 68, 69, 82, 85, 89 and 92 apply here as well. Thus, not only does the specification provide a sufficiently detailed written description, one skilled in the art can practice the invention to the full breadth as claimed, as guidance as to amino acid sequences that exhibit the claimed binding capacities may be found, for example, by examining a relevant database to find sufficiently similar sequences and routine procedures may be utilized, without undue experimentation, to determine whether the invention may be practiced with these sequences. Applicant notes herein that claims 32 and 52 relating to methods for increasing the transduction efficiency have been amended to indicate that the method is performed *in vitro*.

Rejection of claims under 35 U.S.C. § 112, second paragraph

It is asserted that claims 37, 52, 57, 62, 85, 89 and 92 are indefinite in the recitation of "sufficiently similar" as it is asserted that the term is relative in meaning and does not contain a reference point for determining the scope of the claims. It is further asserted that the term "primitive" in these claims is indefinite because it is asserted that the metes and bounds of the term is not apparent.

In reference to the rejection relating to the term "sufficiently similar", one skilled in the art would know the scope of the invention by reviewing, for example, the entire claim that includes such a recitation. For example, the amino acid sequences in question are recited as sufficiently similar to the recited amino acid sequences so that they exhibit either the ability to bind retroviruses or primitive hematopoietic cells. As mentioned above, routine procedures exist for determining whether a particular sequence found in a database search has the desired binding activity and may be utilized in the invention.

In reference to the rejection relating to the term "primitive" as in "primitive hematopoietic cells", applicant asserts that that these cell types are known in the

art and generally refer, as well known in the art, to hematopoietic cells that are in a less developed state.

It is further asserted that claims 23, 33, 41, 49, 55, 60 and 65 are indefinite as it is asserted that the recitation of "low" in "low density" (referring to low density mononuclear cells) is relative in meaning and does not identify the intended scope of the claims. Applicant asserts that low density mononuclear cells are well known to the skilled artisan, and that such an artisan would therefore know the intended scope of the claims.

Claim 47 is objected to as it is asserted "rcombinant" should be typed as "recombinant". Applicant has reviewed claim 47 and the term "recombinant" is spelled "recombinant" and is therefore not misspelled as asserted in the Action.

Withdrawal of the rejection of claims 23, 33, 37, 41, 49, 52, 55, 57, 60, 62, 65, 82, 85, 89 and 92 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Rejection of claims under 35 U.S.C. § 102(b)

Claims 11-13, 23, 26, 28, 29, 31-33, 36-41, 43, 52, 57, 58, 68, 69, 79-83, 87-89, 91 and 92 stand rejected as it is asserted they are anticipated by either Williams et al. [Blood Cells, 20:504-516 (1994)] or Moritz et al. [Moritz et al., J. Clin. Invest. 93:1451-1457 (1994)]. As the Moritz et al. reference was published in April, 1994, which is after the priority date of March 25, 1994 that at least the majority of the rejected claims are entitled to priority to, Moritz et al. is not prior art to these rejected claims under 35 U.S.C. § 102(b). Moreover, as the Williams et al. reference represents the inventor's own work and was published less than one year (January, 1994) prior to the March 25, 1994 priority date of the rejected claims, the Williams et al. reference is not prior art to the rejected claims under 35 U.S.C. § 102(b). Additionally, as to claim 83, there is no teaching or suggestion of utilizing recombinant fibronectin fragments H-296 or CH-296, or that the amount of gene transfer in accordance with the methods of the current invention, when conducted with those fragments, is superior as seen, for

example, in FIG. 10. Withdrawal of the rejections of claims 11-13, 23, 26, 28, 29, 31-33, 36-41, 43, 52, 57, 58, 68, 69, 79-83, 87-89, 91 and 92 under 35 U.S.C. § 102(b) is respectfully requested.

Claims 68, 69 and 79-83 stand rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,354,686 to Haberman. Haberman is relied on fo teaching a method for transducing T cells with a retrovirus that includes infecting the cells with a retrovirus in the presence of a supporting material that includes any known extracellular proteins including fibronectin.

Contrary to the assertions in the Action, Haberman describes substantially purified mature T cells that are capable of binding to extracellular matrix proteins. As recited in column 38, lines 22-39 of the Haberman reference, Haberman also teaches methods for exploiting the capacity of various T cells to localize to a site and, via binding to extracellular matrix proteins at the site, to express and produce lymphokines. There is no teaching or suggestion of utilizing extracellular matrix proteins to increase transduction efficiency or gene transfer as recited in claims 79, 80 and the claims dependent thereon. Additionally, Haberman does not teach or suggest the methods for localizing a virus as recited in claims 68 and 69. Withdrawal of the rejection of claims 68, 69, and 79-83 under 35 U.S.C. § 102(b) is respectfully requested.

Rejection of claims under 35 U.S.C. § 102(e) or 35 U.S.C. § 103(a)

Claims 11-14, 16, 23-39, 44, 45, 47-50, 52-53, 56-58, 62, 63, 67-69 and 79-83 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Lim et al. [PNAS, 86:8892-8896 (1989)], Moritz et al. above, U.S. Patent No. 5,686,278 to Williams et al. and U.S. Patent No. 6,051,427 to Finer et al. As the rejected claims are entitled to the priority date of March 25, 1994, ultimately based on the filing date of U.S. Patent No. 5,686,278 to Williams et al., the '278 patent is not considered prior art to the pending claims. As at least the majority of previously mentioned herein, based on this same priority date, the Moritz et al. reference is not considered prior art to these pending claims. Additionally, as U.S. Patent No. 6,051,427 was filed on August 21, 1995, which is after the priority filing date of

March 25, 1994 (as well as after the date of filing of the PCT application which is a continuation-in-part of the '427 patent and was filed March 27, 1995), the '427 patent is not considered prior art to the pending claims. Moreover, as the Lim et al. reference by itself does not teach or suggest the methods or cellular populations recited in the pending claims, withdrawal of the rejection of claims 11-14, 16, 23-39, 44, 45, 47-50, 52-53, 56-58, 62, 63, 67-69 and 79-83 under 35 U.S.C. § 103(a) is respectfully requested.

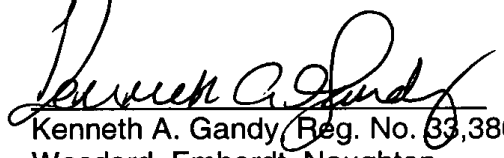
Claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89 and 91-93 stand rejected under 35 U.S.C. § 102(e) as being anticipated by, or in the alternative, under 35 U.S.C. § 103(a), as being unpatentable over either the Williams et al. '278 patent or the Finer et al. '427 patent. These references are not considered prior art to at least the majority of the pending claims. Additionally, as to claim 83, these references do not teach the use of the recombinant CH-296 and H-296 fragments, or their advantageous performance. Withdrawal of the rejection of claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89 and 91-93 under either 35 U.S.C. § 102(e) or 35 U.S.C. §103(a) is thus respectfully requested.

Double patenting rejection

Claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89 and 91-93 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-20 of U.S. Patent No. 5,686,278 or claims 1-14 over U.S. Patent No. 6,033,907. Terminal disclaimers are in preparation and will be submitted to overcome this rejection. Withdrawal of the double patenting rejection of claims 11-23, 26-43, 52-61, 68, 69, 79-83, 87-89 and 91-93 is respectfully requested.

In view of the foregoing, it is submitted that all of the rejections have been overcome and that the application is in condition for allowance. Action to that end is solicited. The Examiner is invited to telephone the undersigned attorney if there are any questions or other matters that might be addressed in that fashion.

Respectfully submitted

By: 

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ADDENDUM

Please amend claims 24, 32, 44, 52, 62, and 84 as follows;

24. (Amended) An improved method for cellular grafting, comprising the steps of:

obtaining viable hematopoietic cells from [an animal] a mammalian donor;

infecting the viable hematopoietic cells with a replication-defective recombinant retrovirus vector containing exogenous DNA to produce transduced viable hematopoietic cells, the infecting being in the presence of an immobilized amount of fibronectin and/or a fragment thereof effective to increase the efficiency of cellular transduction by the retrovirus vector; and

introducing the transduced viable hematopoietic cells into [an animal] a mammalian recipient as a cellular graft.

32. (Amended) A method for increasing the frequency of transduction of hematopoietic cells in vitro by a replication-defective recombinant retrovirus vector, comprising infecting a population of viable hematopoietic cells enriched in hematopoietic stem cells with a replication-defective recombinant retrovirus vector in the presence of an effective immobilized amount of polypeptide containing a first amino acid sequence which provides the binding activity of the Heparin-II binding domain of fibronectin and a second amino acid sequence which provides the cell-binding activity of the CS-1 domain of fibronectin, to increase the frequency of transduction of the hematopoietic cells by the retrovirus vector.

44. (Amended) A cellular grafting method, comprising:

introducing into [an animal] a mammal as a cellular graft, viable hematopoietic cells transduced by retroviral-mediated gene transfer in the absence of retroviral producer cells and in the presence of an immobilized amount of a polypeptide containing a first amino acid sequence which provides the binding activity of the Heparin-II binding domain of fibronectin and a second amino acid sequence which provides the cell-binding activity of the CS-1 domain of fibronectin, said immobilized

amount of polypeptide being effective to increase the frequency of transduction of the hematopoietic cells by the retrovirus vector.

52. (Amended) A method for increasing the frequency of transduction of hematopoietic cells in vitro by a replication-defective recombinant retrovirus vector, comprising infecting hematopoietic cells with a replication-defective retrovirus vector in the presence of an effective immobilized amount of a recombinant polypeptide containing a first amino acid sequence represented by the formula:

Ala Ile Pro Ala Pro Thr Asp Leu Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr

or a sufficiently similar amino acid sequence thereto to exhibit the ability to bind retroviruses;

and a second amino acid sequence represented by the formula:

Asp Flu Leu Pro Gln Leu Val Thr Leu Pro His Pro Asn Leu His Gly Pro Glu Ile Leu Asp Val Pro Ser Thr

or a sufficiently similar amino acid sequence thereto to exhibit the ability to bind primitive hematopoietic cells.

62. (Amended) A cellular grafting method, comprising:

introducing into [an animal] a mammal as a cellular graft, viable hematopoietic cells transduced by retroviral-mediated gene transfer in the absence of retroviral producer cells and in presence of an effective immobilized amount of a recombinant polypeptide which increases the frequency of transduction of the hematopoietic cells, said recombinant polypeptide containing a first amino acid sequence represented by the formula:

Ala Ile Pro Ala Pro Thr Asp Leu Lys Phe Thr Gln Val Thr Pro Thr Ser Leu Ser Ala Gln Trp Thr Pro Pro Asn Val Gln Leu Thr Gly Tyr Arg Val Arg Val Thr Pro Lys Glu Lys Thr Gly Pro Met Lys Glu Ile Asn Leu Ala Pro Asp Ser Ser Ser Val Val Val Ser Gly Leu Met Val Ala Thr Lys Tyr Glu Val Ser Val Tyr Ala Leu Lys Asp Thr Leu Thr Ser Arg Pro Ala Gln Gly Val Val Thr Thr Leu Glu Asn Val Ser Pro Pro Arg Arg Ala Arg Val Thr Asp Ala Thr Glu Thr Thr Ile Thr Ile Ser Trp Arg Thr Lys Thr Glu Thr Ile Thr Gly Phe Gln Val Asp Ala Val Pro Ala Asn Gly Gln Thr Pro Ile Gln Arg Thr Ile Lys Pro Asp Val Arg Ser Tyr Thr Ile Thr Gly Leu Gln Pro Gly Thr Asp Tyr Lys Ile Tyr Leu Tyr Thr Leu Asn Asp Asn Ala Arg Ser Ser Pro Val Val Ile Asp Ala Ser Thr Ala Ile Asp Ala Pro Ser Asn Leu Arg Phe Leu Ala Thr Thr Pro Asn Ser Leu Leu Val Ser Trp Gln Pro Pro Arg Ala Arg Ile Thr Gly Tyr Ile Ile Lys Tyr Glu Lys Pro Gly Ser Pro Pro Arg Glu Val Val Pro Arg Pro Arg Pro Gly Val Thr Glu Ala Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu Tyr Thr Ile Tyr Val Ile Ala Leu Lys Asn Asn Gln Lys Ser Glu Pro Leu Ile Gly Arg Lys Lys Thr

or a sufficiently similar amino acid sequence thereto to exhibit the ability to bind retroviruses;

and a second amino acid sequence represented by the formula:

Asp Glu Leu Pro Gln Leu Val Thr Leu Pro His Pro Asn Leu His Gly Pro Glu Ile Leu Asp Val Pro Ser Thr

or a sufficiently similar amino acid sequence thereto to exhibit the ability to bind primitive hematopoietic cells.

84. (Amended) An improved method for cellular grafting, comprising the steps of:

obtaining viable mammalian cells from an animal donor;

infecting the cells with a replication-defective recombinant retrovirus vector containing exogenous DNA to produce transduced cells, the infecting being in the presence of an immobilized amount of fibronectin and/or a fragment thereof effective to increase the efficiency of cellular transduction by the retrovirus vector; and

introducing the transduced cells into [an animal] a mammalian recipient as a cellular graft.